

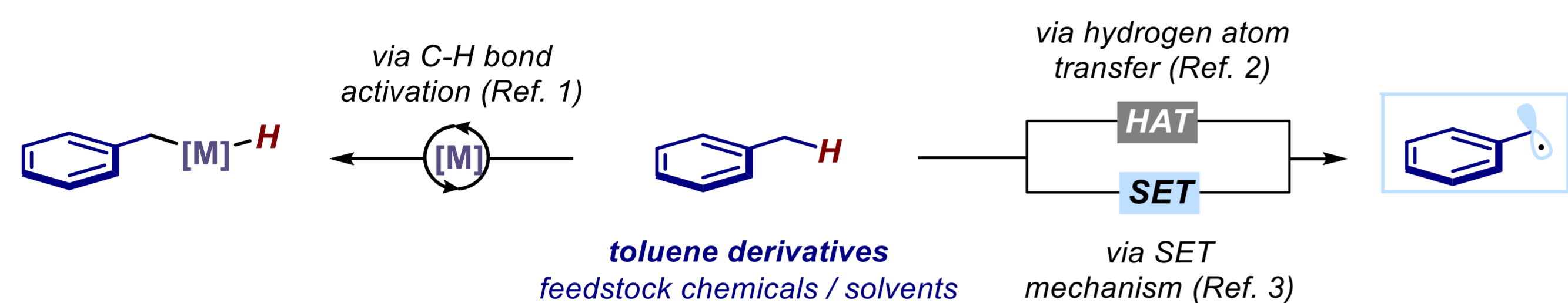
Direct Asymmetric C–H Functionalization of Toluene Derivatives via Excited Iminium Ions Catalysis

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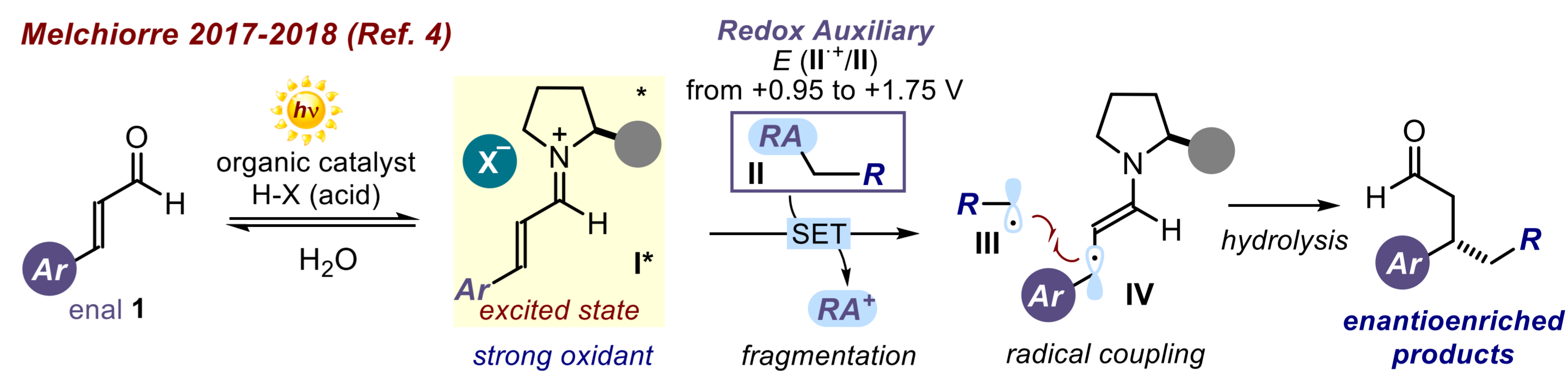
C(sp³)-H Functionalization of Toluene and Derivatives

- Previous Strategies:

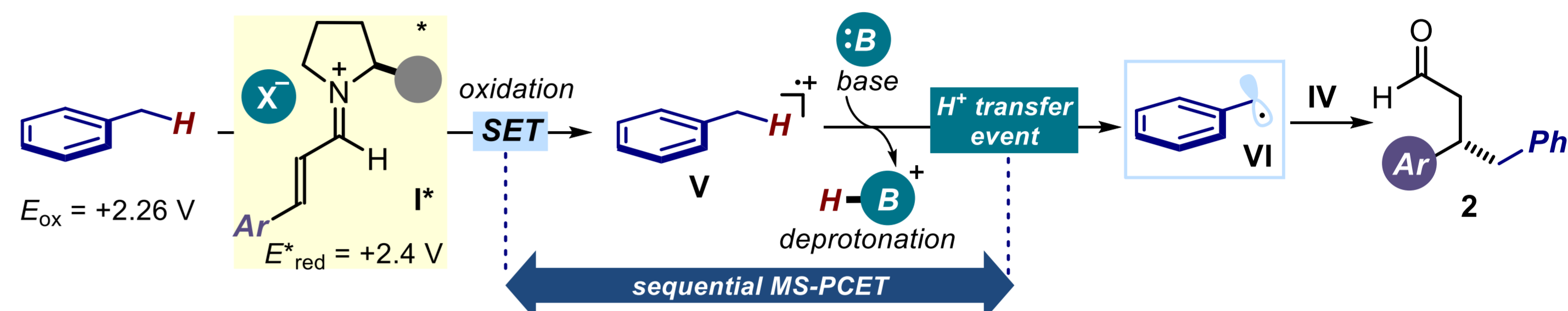


- Direct functionalization of highly available feedstock chemicals
- Few examples of insertion into benzylic C(sp³)-H bonds (selectivity issues)
- Mainly achieved through radical pathways (HAT, SET)
- Use of toluene in enantioselective catalysis: elusive

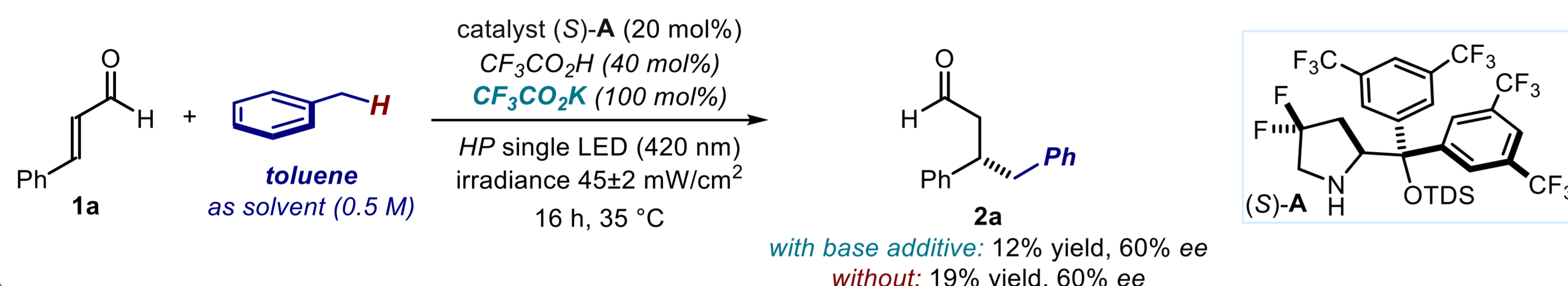
- Our Strategy:



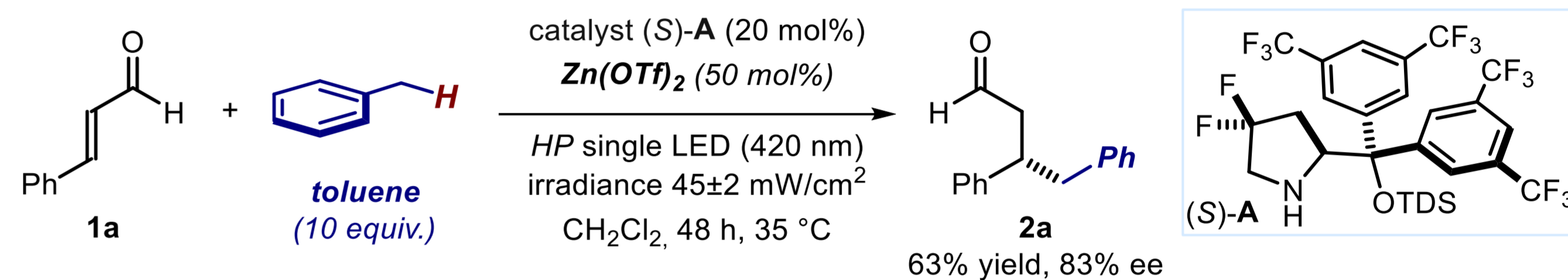
This Study: Use of Toluene in Enantioselective Catalysis



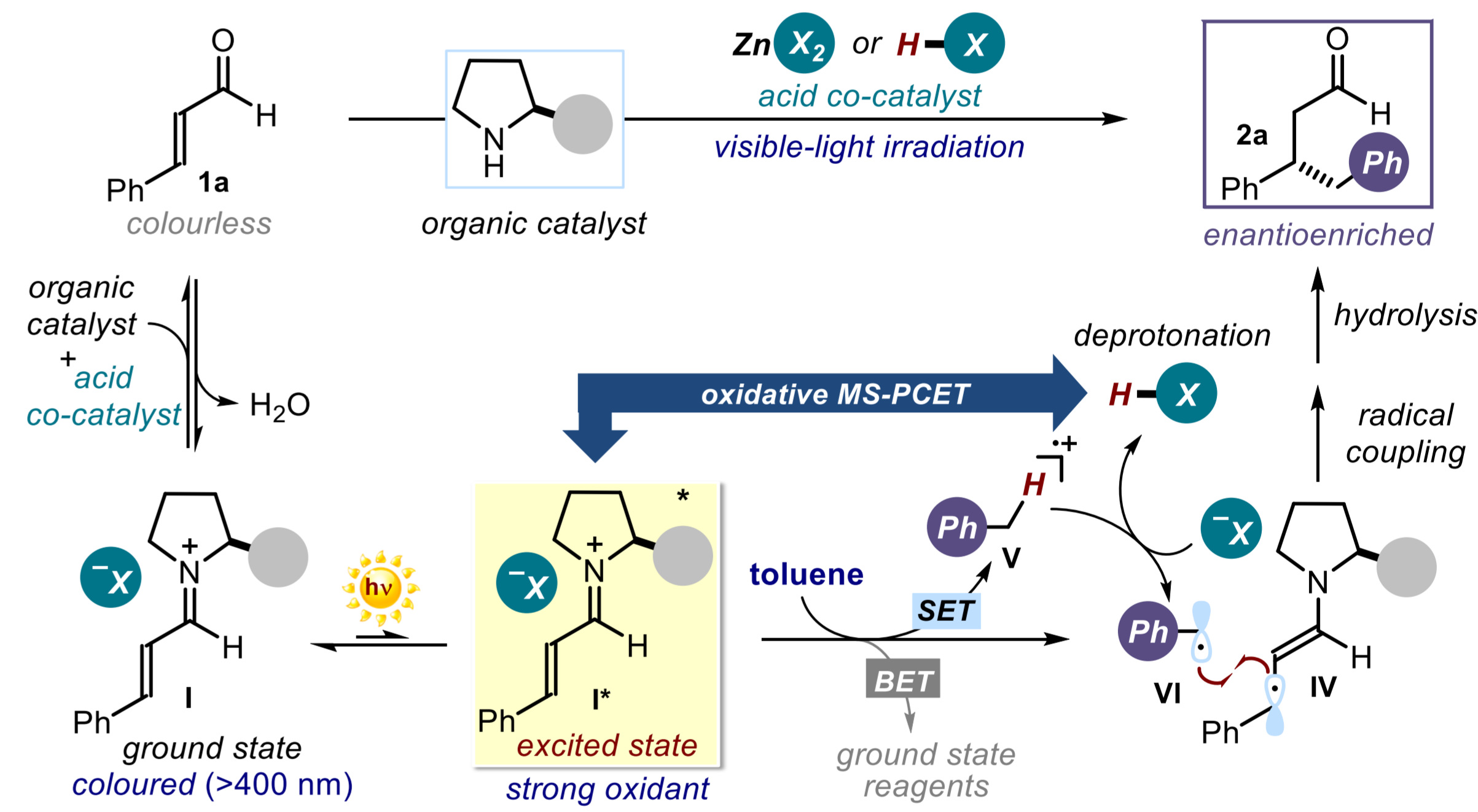
Preliminary Studies



Optimized Conditions

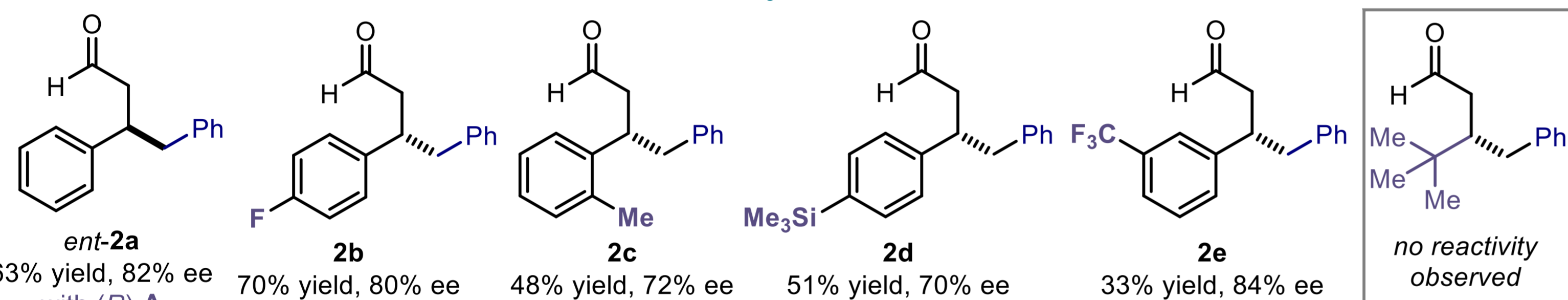


- Proposed Mechanism:

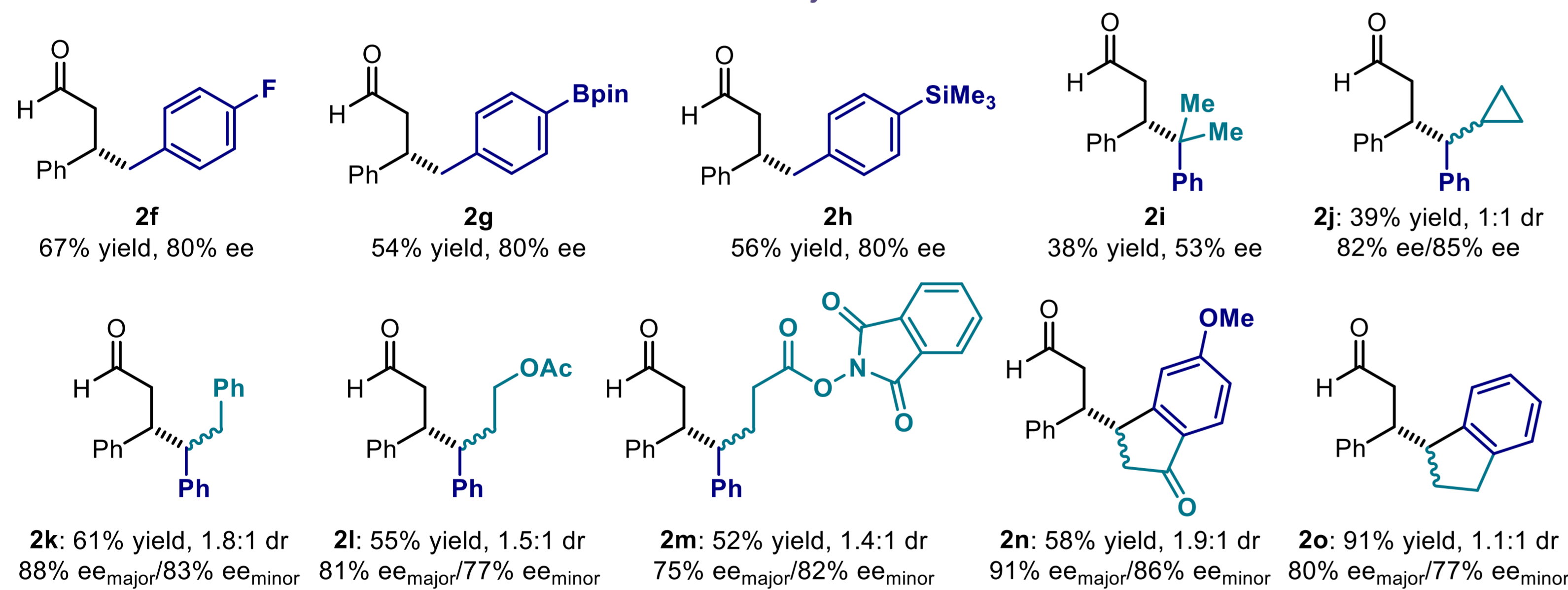


Substrate Scope

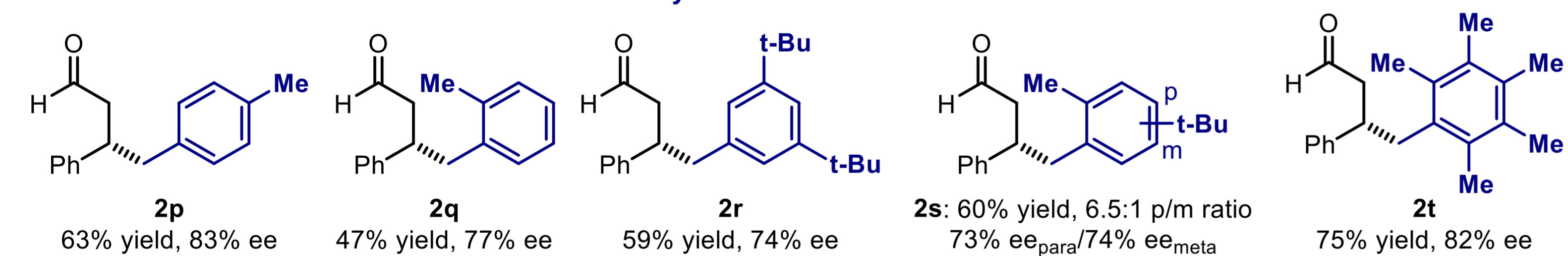
Cinnamaldehyde Derivatives



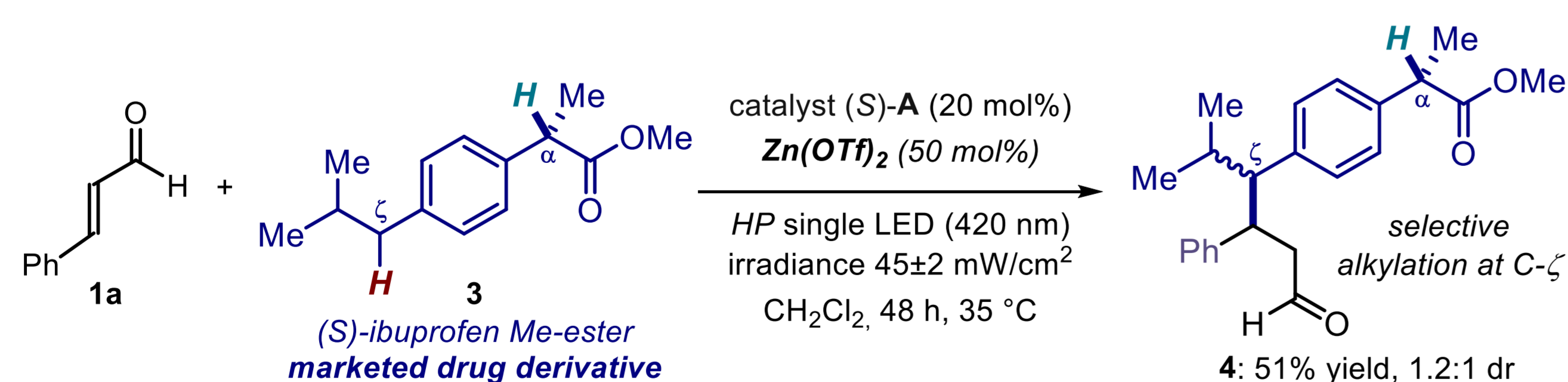
Toluene and Benzylic Derivatives



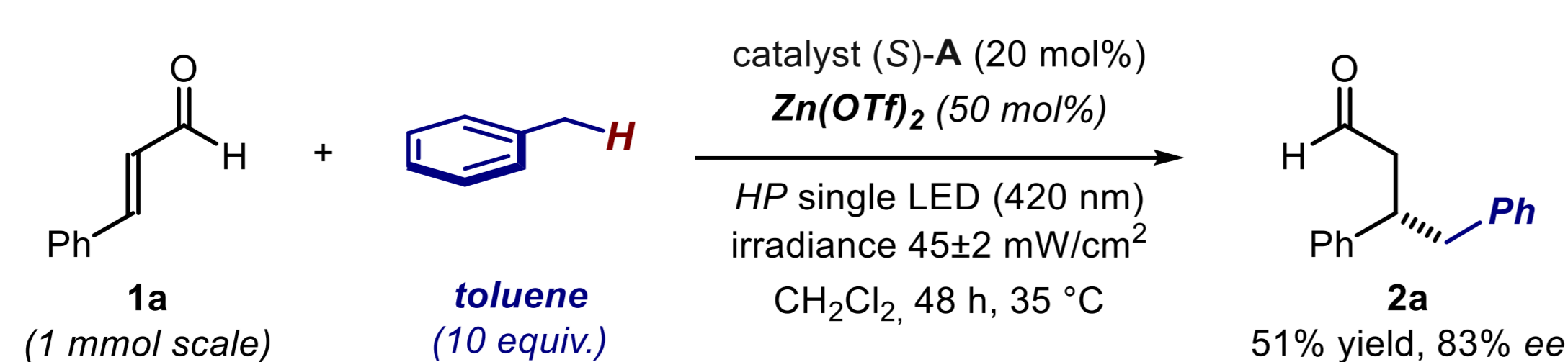
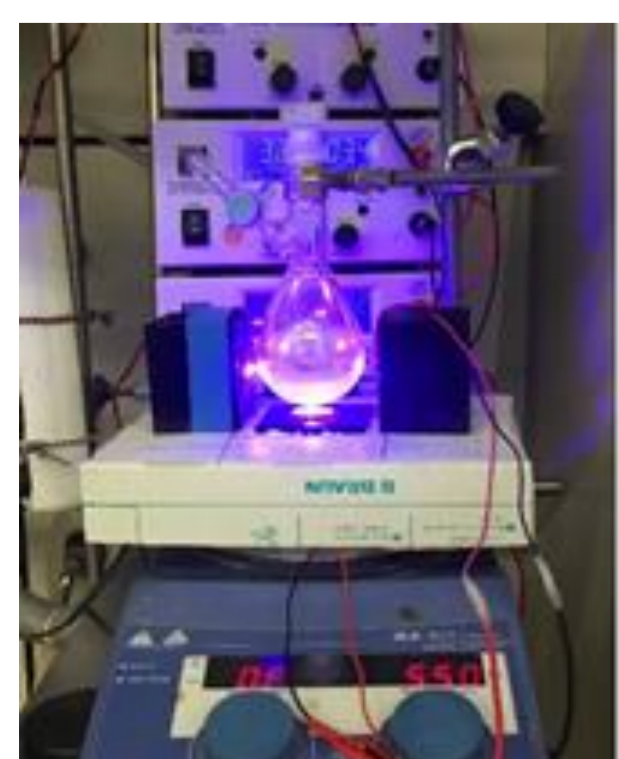
Xylene and Derivatives



Selective Functionalization of Pharmaceuticals

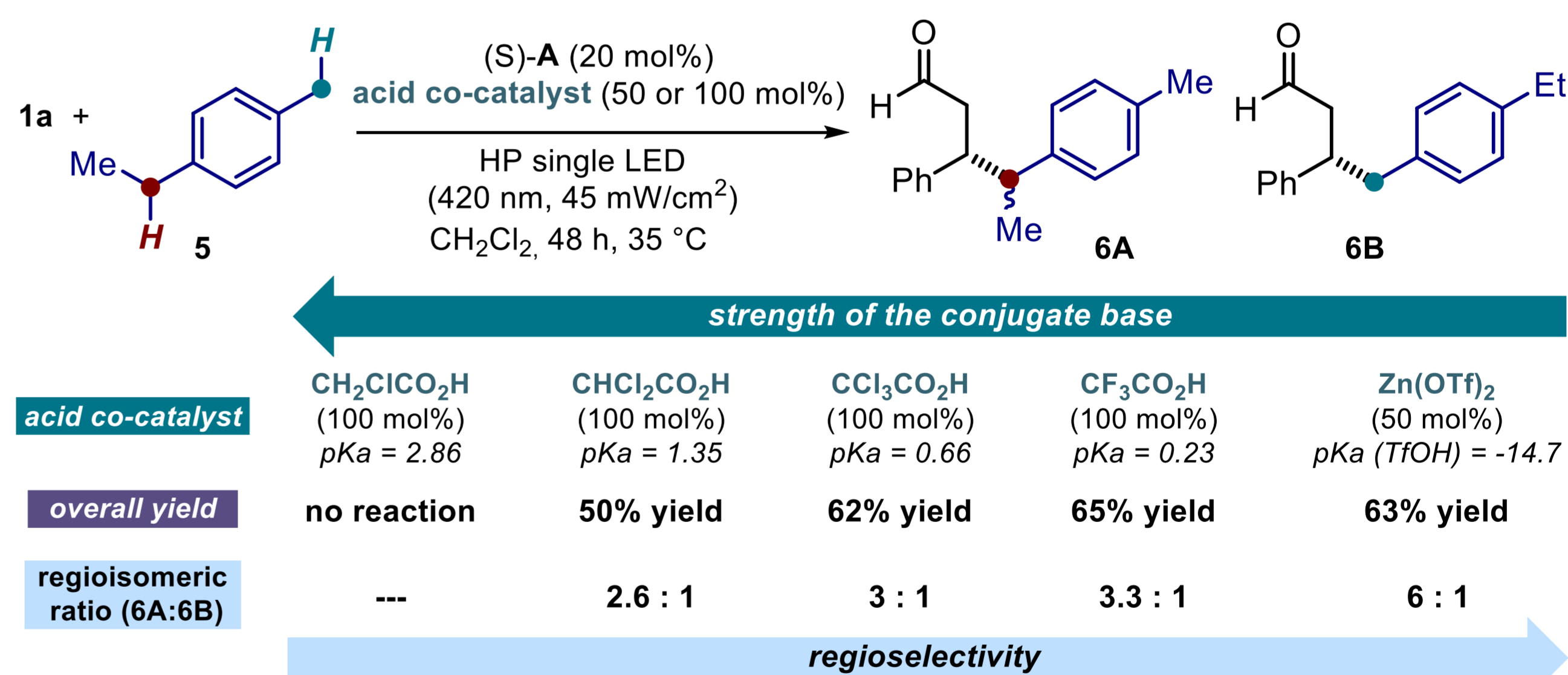


Methodology Scale-up

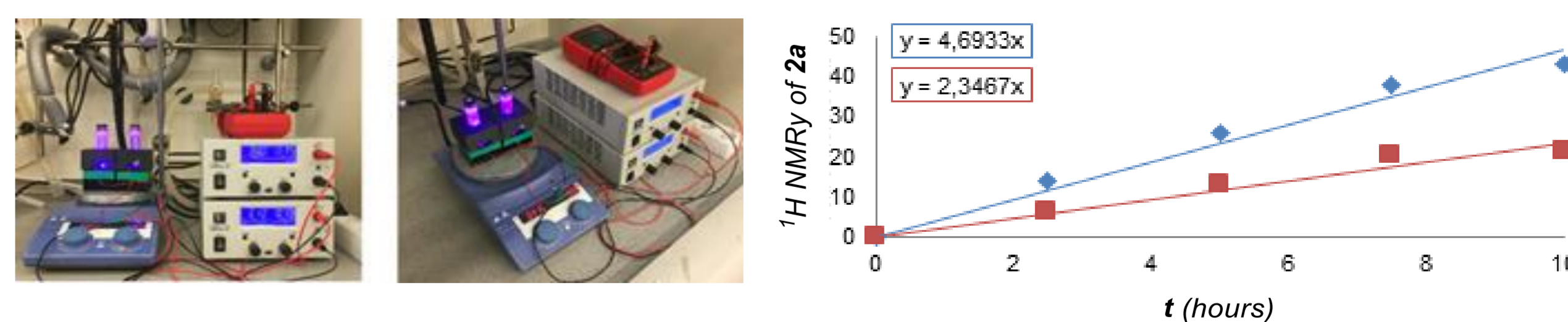


Mechanistic Insights

- Selectivity Study:



- KIE Determination (2.00): benchmark reactions between 1a and either toluene or toluene-d₈ under standard conditions



References:

- (1) a) *Org. Lett.* **2013**, *15*, 4098; b) *J. Org. Chem.* **2002**, *67*, 4165.
(2) a) *J. Am. Chem. Soc.* **2014**, *136*, 15509; b) *Adv. Synth. Catal.* **2013**, *355*, 2891.
(3) a) *Chem. Sci.* **2017**, *39*, 3845-3879; b) *Chem. Commun.* **2010**, *46*, 601.
(4) a) *ACS Catal.* **2018**, *8*, 1062; b) *Angew. Chem., Int. Ed.* **2018**, *57*, 1068; c) *Nat. Chem.* **2017**, *9*, 868.

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